

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference WOB02 IDM CD8T	FOR FURTHER ACTION	
See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)		
International application No. PCT/EP 03/13579	International filing date (day/month/year) 02.12.2003	Priority date (day/month/year) 03.12.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/50, C12Q1/68		
Applicant DARTMOUTH COLLEGE et al.		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>	
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 	

Date of submission of the demand 19.05.2004	Date of completion of this report 20.04.2005
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I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-70 as originally filed

Claims, Numbers

) 1-49 as originally filed

Drawings, Sheets

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

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5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 1-26, 45
 - because:
 - the said international application, or the said claims Nos. 1-26 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos. 45
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - the written form has not been furnished or does not comply with the Standard.
 - the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	27-44, 46-49
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	27-44, 46-49
Industrial applicability (IA)	Yes: Claims	27-44, 46-49
	No: Claims	

2. Citations and explanations

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see separate sheet

Section III:

1. Claims 1 to 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(v) PCT.

Claims 1 to 26 concern a method of characterizing a T cell response of a final population of T-lymphocytes which method defines the parameters to be measured and how data is to be treated. The result of the method is the characterization of the final population of T-lymphocytes by classification into a number of subsets related to the number of parameters measured. Said method however lacks a technical character because the subject-matter of each claim as a whole does not cause any technical effect.

Consequently no opinion will be formulated on the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. The subject-matter of claim 45 has not been searched. Consequently, no opinion will be established on the subject-matter of said claim (Rule 66.1(e) PCT).

Section V:

Reference is made to the following documents cited in the International search report:

- D1: GIVAN ALICE ET AL: "A flow cytometric method to estimate the precursor frequencies of cells proliferating in response to specific antigens" CYTOMETRY SUPPLEMENT, no. 10, 2000, page 94, XP002278599 & THE XX CONGRESS OF THE INTERNATIONAL SOCIETY FOR ANALYTICAL CYTOLOGY; MONTPELLIER, FRANCE; MAY 20-25, 2000 ISSN: 1046-7386
- D2: ALLSOPP C E M ET AL: "A flow cytometric method to assess antigen-specific proliferative responses of different subpopulations of fresh and cryopreserved human peripheral blood mononuclear cells" JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 214, no. 1-2, 1 May 1998 (1998-05-01), pages 175-186, XP004129949 ISSN: 0022-1759
- D3: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE,

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PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), ZAKI MOHAMED H ET AL: "Non-Neoplastic T Cells from B-CLL Patients Exhibit Intrinsic Defects in TCR Signaling." XP002278601 Database accession no. PREV200300336083

- D4: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), RUBIO MARIE T ET AL: "Use of CFSE and Intracellular Cytokine Staining To Detect CD8 T Cell Response to Exogenous Protein Antigen Presented by Monocyte-Derived Human Dendritic Cells: Differential Effects of PGE2 on Antigen Presentation to CD4 Versus CD8 T Cells." XP002278602 Database accession no. PREV200300356793
- D5: BERCOVICI N ET AL: "Multiparameter precursor analysis of T-cell responses to antigen" JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 276, no. 1-2, 1 May 2003 (2003-05-01), pages 5-17, XP004422637 ISSN: 0022-1759

1. Independent claims 27, 31, 34, 37, 39, 40, 42, 43, 46 and 47 concern methods making use of the method of analysing a T cell response as defined in claim 1. However, said method of analysing a T cell response is not novel (see below). Since the uses defined in said claims are obvious uses of a method of analysing a T cell response, the uses as defined in the claims 27, 31, 34, 37, 39, 40, 42, 43, 46 and 47 do not involve an inventive step. Therefore, said claims do not seem to comply with the requirements of Article 33(3) PCT.

D1 discloses a flow cytometric method to estimate the precursor frequencies of cells proliferating in response to specific antigens (see abstract). D1 shows the measurement of two parameters by flow cytometry and back-calculation to the frequency of cells in the original population (see p.101, first paragraph to p.1055, right-hand column, first paragraph and Fig.1). Therefore claim 1 is not novel (Article 33(2) PCT).

Dependent claims 2 to 6 and 8 to 26 do not seem to contain any features which render them inventive.

Dependent claim 7 concerns the method of back-calculation of the precursor cell population. This method is not disclosed in any of the cited documents. However, no technical effect seems to be associate with this method of calculation, so that this

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feature does not seem to render the method inventive (Article 33(3) PCT).

Consequently, claims directed to obvious uses of a method of analysing a T cell response (see also the uses already explicitly suggested in D1, last full sentence of abstract), the method itself not being novel as discussed in the paragraph above, do not involve an inventive step, as outlined above for claims 27, 31, 34, 37, 39, 40, 42, 43, 46 and 47 (Article 33(3) PCT).

The dependent claims 28 to 30, 32, 33, 35, 36, 38, 41, 44 and 49 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

2. The same objections as under point 1 apply in view of any of D2 to D4.
Any of D2 to D4 disclose multiparameter cytometric analysis of T cells and back-calculation to precursor frequencies (see D1, abstract, p.178, left-hand column, paragraph 2 to p.181, right-hand column, first paragraph and Figs 2 to 4; D3, abstract; D4, abstract). D1 discloses the use of PKH26 dye to determine lymphocyte proliferative responses to the antigen tetanus toxoid, in combination with cell phenotyping and measurement of cytokine production at the single cell level (see abstract).
Thus, the subject-matter of claims 27 to 44 and 46 to 49 does not involve an inventive step (Article 33(3) PCT).

3. Document D5, cited in the International search report as an intermediate document, may be detrimental to the novelty and inventiveness of the subject-matter of the present claims if the priority date of 3 December 2002 is not validly claimed by the present application.